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| protocol |
| HABIT-ILE: A RANDOMISED TRIAL OF HAND ARM BIMANUAL INTENSIVE TRAINING INCLUDING LOWER EXTREMITY TRAINING FOR CHILDREN WITH BILATERAL CEREBRAL PALSY |
| Protocol Number: APP1144846Version: 1.0Date: 2/11/2017 |
|  |
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| **CONFIDENTIAL**This document is confidential and the property of Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland. No part of it may be transmitted, reproduced, published, or used without prior written authorization from the institution.**Statement of Compliance**This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95). |

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## **Glossary of Abbreviations & Terms**

|  |  |
| --- | --- |
| **Abbreviation** | **Description (using lay language)** |
| 95% CI | Ninety Five Percent Confidence Interval |
| 6MWT | 6 minute walk test |
| AEs | Adverse Events |
| AI | Associate Investigator |
| BOLD | Blood Oxygen Level Dependent |
| CHU-9D | The Child Health Utility 9D |
| CI | Chief Investigator |
| CONSORT | Consolidated Standards of Reporting Trials |
| COPM | Canadian Occupational Performance Measure |
| CP | Cerebral Palsy |
| CS | Corticospinal |
| CSF | Cerebrospinal fluid |
| ES | Effect Size |
| fMRI | Functional Magnetic Resonance Imaging |
| GM | Gray matter |
| GMFCS | Gross Motor Function Classification System |
| HABIT | Hand Arm Bimanual Intensive Training |
| HABIT-ILE | Hand Arm Bimanual Intensive Training Including Lower Extremity Training |
| HARDI | High Angular Resolution Diffusion Imaging |
| ICERs | Incremental Cost Effectiveness Ratios |
| GMFM | Gross Motor Function Measure |
| MCID | Minimal clinical important difference |
| MD | Mean Difference |
| NDIS | National Disability Insurance Scheme |
| NEAF | National Ethics Application Form |
| NHMRC | National Health Medical Research Council |
| NSW | New South Wales |
| PEDI-CAT | Pediatric Evaluation of Disability Inventory – Computer Adapted Test |
| QLD | Queensland |
| RCT | Randomised Controlled Trial |
| SD | Standard Deviation |
| SPIRIT | Standard Protocol Items: Recommendations for Intervention Trials |
| T1 | Time point 1: Baseline |
| T2 | Time point 2 |
| T3 | Time point 3 |
| T4 | Time point 4 |
|  WA | Western Australia |
| WM | White matter |

## **Study Sites**

### Study Location/s

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
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|  |  |  |  |  |
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## **Funding and Resources**

### Source/s of Funding

NHMRC Project Funding APP1144846 for $1, 100, 902.90

## **Introduction/Background Information**

### Lay Summary

In Australia, 35,000 people have cerebral palsy (CP), and between 60-70% of these have difficulties with movement on both sides of their body. There are currently no effective interventions for children with CP that affects both sides of their body to improve their ability to use their hands, walk and perform daily life tasks. We have promising data about a new intervention, called Hand Arm Bimanual Intensive Training Including Lower Extremity (HABIT-ILE), which we will test in 126 children with cerebral palsy and compare results to usual care.

4.2 Introduction

Six hundred children are newly diagnosed with cerebral palsy (CP) each year, with >35,000 people living with CP in Australia1. Over 61% of children with CP have “bilateral” motor involvement, impairing movement on both sides of the body2. For these children, 75% cannot walk or use their arms effectively, impacting their future independence and participation in home, school, work and community life3. There is a paucity of evidence for effective interventions to improve motor outcomes for children with bilateral CP.

Our team has conducted four RCTs to understand intensity, dose and type of effective upper limb training for children with unilateral CP4-7. In bilateral CP, children need high intensity training for both upper and lower limbs, but few treatment options exist. We now have a new treatment approach for bilateral CP that targets training both the left and right upper and lower limbs, based on learnings from our successful unilateral CP research8. This treatment combines Hand Arm Bimanual Intensive Training (HABIT) Including Lower Extremity training- “HABIT-ILE”9,10. This treatment has now been pilot tested for children with bilateral CP (n=20), demonstrating significant improvements in manual ability with a 1.6 logit gain on the ABILHAND-Kids (p<0.001) and gross motor function with a 7 point (> minimally clinically important difference MCID of 3.5) increase on the Gross Motor Function Measure (p<0.001)11. We now propose a definitive randomised trial of HABIT-ILE in 126 children with bilateral CP. This will be the largest motor training study in bilateral CP ever conducted internationally. As a secondary outcome, we will incorporate our state of the art protocol of advanced MRI to investigate brain structural integrity, and functional and structural connectivity (using fMRI guided diffusion MRI tractography)12-15

### Background information

**Promoting independence and quality of life for Australians with cerebral palsy**

In Australia, CP is the most common physical disability in childhood2. People with CP have poorer health outcomes (<1.9 standard deviations on the Physical Summary Score of the Child Health Questionnaire) compared to age matched peers19. Increased severity of physical disability is associated with reduced general health, greater pain and discomfort19, reduced independence in daily life skills20 and poorer vocational outcomes21. Interventions that reduce the impact of the physical disability and promote independence in daily life skills, inclusion and community participation is a major priority area of the National Disability Strategy.

**Intensive upper and lower extremity training may enhance motor performance and independence in daily life activities for children with bilateral CP**

Intense, specific, integrated upper and lower extremity training that harnesses activity-dependent neuroplasticity using principles of motor learning is a novel intervention that may lead to improved mobility, manual ability, and independence in daily life activities for children with bilateral CP.

**Evidence for interventions to enhance motor performance in children with bilateral CP**

Traditional neurodevelopmental interventions are frequently based on passive movement experiences and with the concept of “normalisation”. These have been shown to be ineffective in improving motor outcomes for children with CP8,22. Contemporary interventions for school-aged children with CP have predominantly targeted upper and lower extremity motor performance separately8,22. To date, significant evidence exists for intensive upper extremity interventions (≈60 hours) to enhance motor performance in children with unilateral CP8. Our group has conducted extensive work (4 RCTs) to confirm the efficacy of intensity, dose and type of effective upper limb training for children with mild to moderate unilateral CP4-7. Our highly cited meta-analysis8 and others22,23 identified growing evidence for intensive contemporary motor learning based approaches to upper limb training for children with unilateral CP (e.g. constraint induced movement therapy, Hand Arm Bimanual Intensive Training [HABIT]) to improve upper limb motor performance compared to usual care. Intensive upper limb training has however not been tested in children with bilateral CP, the largest subgroup of CP. Interventions to target lower compared to upper limb motor performance have generally been less intensive. A recent systematic review identified specific gait training was effective in increasing gait speed for children with unilateral and bilateral CP (Effect Size ES 0.92; p=0.01), whereas resistance training was not24. One model of intervention was developed for children with unilateral CP which integrates Hand Arm Bimanual Intensive Training and Including Lower Extremity training (HABIT-ILE)9-11. HABIT-ILE is based on known principles of how to induce neuroplasticity including specific, intensive, repetitive task practice. HABIT-ILE has demonstrated strong effects to improve manual ability on the ABILHAND Kids (ES 1.54; p<0.01) and walking speed on the 6 Minute Walk Test (6MWT; ES 0.9; p=0.04). Evidence indicates that motor learning based interventions for children with CP need to be intensive, specific, repetitive, incremental and challenging in order to improve motor performance.

**Evidence from advanced brain imaging in children with CP**

The importance of a multilevel network in the reorganisation of the corticospinal system has been suggested by our work in unilateral CP13,14. The developing connectivity and symmetry of the thalamocortical pathways connecting M1 with the thalamus is as important as the symmetry of the cortico-spinal (CS) tracts for unimanual capacity and bimanual co-ordination14,25. High Angular Resolution Diffusion Imaging (HARDI) can be performed to elucidate symmetry in the CS (motor) and thalamocortical (sensorimotor) tracts, ideally using our surface-based fMRI-guided seeding approaches, which are more accurate than traditional approaches using anatomically defined seed regions (Fig. 2). Our approach relies on selecting a particular region of interest based on changes in signal during blood oxygen level dependent (BOLD) contrast MRI during motor tasks carefully selected to activate particular regions of the brain as the source for white-matter pathways to project through the brain13. The projected paths are subsequently characterised in terms of the speed with which water diffuses in the region of the tract (mean diffusion) and how much a particular direction is favoured (anisotropy). The fMRI-guided approach results in a better definition of the extracted pathways compared to traditional approaches, where the entire motor strip is used as a seed region. Additionally, in children with CP, the location of the motor region may be shifted compared to typically developing children. fMRI-guided tractography is therefore particularly suited for this population13.

Fig 1Tractography of the corticospinal tract (left) is more accurate when seeded using fMRI-guided techniques13 (right)



Surprisingly, the sensorimotor thalamic tracts have been found to be more significantly correlated with paretic hand functions than the CS tracts14. These data suggest functional outcome is not only related to the integrity of the CS tract but also requires feedback from sensory systems to shape the motor cortex and underlying pathways14. **Additionally, our MRI work26 with children with unilateral CP and others27-29 validates that children with CP have cortical plasticity.**

Structural changes, including greater cortical thickness on the contra-lesional hemisphere in children with unilateral CP, have been observed, illustrating possible compensatory mechanisms30. Recently, we have found that even subtle changes in morphology and microstructure (diffusion tractography) can be detected31. Critical to detecting subtle changes in morphology pre- and post-therapy is to delineate regions of interest in a manner that does not bias measurements with respect to either time point. This is typically performed by delineating regions of interest on a temporally unbiased structural image that is generated by registering images from both time points. ROIs delineated in this manner can then be propagated back to each scan (Fig. 3). At this point, it is possible to obtain segmentations of white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF). Due to the large extent of abnormality typical to children with CP, existing state-of-the-art approaches to automatically segment the brain tissue fail, so we utilise a unique approach that removes the reliance on atlas data with the best published results for children with CP30,32-34. From the grey matter segmentation, the inner and outer surfaces of the cortex can be extracted directly30. Our uniquely accurate approaches will be utilised to examine the pattern of observed changes in cortical thickness in children that undergo HABIT-ILE. This is important, because whether CP is unilateral or bilateral, the location of lesions and the pattern of recovery in response to therapy may vary. While the benefits of therapy are now clear, the mechanisms behind it are less so. A deeper understanding into what form neural remodelling takes is critical to achieving further optimisation of therapy. Tools are now available to detect and characterise the subtle anatomical and physiological changes that are associated with the beneficial effects of therapy.

Fig 2. Delineations of key regions of interest should be performed in a medial space before computing mean measure such as cortical thickness within each propagated region.

**Pilot data, which supports this new RCT**

A novel intensive intervention integrating upper and lower extremity training, HABIT-ILE which was originally designed for children with unilateral CP9, was modified and pilot tested by CIC in a quasi-randomised trial with 20 children with bilateral CP11. HABIT-ILE is an intensive upper limb bimanual training approach that continuously challenges lower extremity function and postural control. Adaptation of some of the content was required to accommodate the additional motor difficulties experienced by children with bilateral CP who as a group had greater challenges with mobility and upper extremity function11. Participants were: (a) Gross Motor Function Classification (GMFCS) Levels II=4, III=14 and IV=2; and (b) mean age 11 yrs SD 4.811.

HABIT-ILE was delivered in groups of 4-6 children, 6.5 hrs/day over 13 days (total dose 84.5 hrs). Compared to a delayed treatment group, children receiving HABIT-ILE achieved significantly greater gains in manual ability (ABILHAND Kids *n*2=0.32; p<0.001), self-care on the PEDI-CAT (*n*2=0.26; p=0.001), gross motor function on the GMFM (*n*2=0.33; p<0.001), walking speed on the 6MWT (*n*2=0.17; p<0.03) and balance on the Pediatric Balance Scale (PBS: *n*2=0.28; p<0.002) (Figure 4).

HABIT-ILE

Control

Fig 4. Gains in manual ability and gross motor functioning following HABIT-ILE compared to usual care

For children receiving HABIT-ILE this equated to significant improvements in manual ability(1.6 logit gain on ABILHAND-Kids), self-care (8 point increase on PEDI-CAT), gross motor function (7 logit increase on GMFM), walking speed (2 metre gain on 6MWT) and balance (11 point gain on the PBS)11.

## **Study Objectives**

### Research Aim

This pragmatic, single-blind randomised controlled trial (RCT) of 126 children with bilateral CP aims to evaluate the effects of HABIT-ILE versus usual care on manual ability and gross motor function immediately post intervention. Secondary outcomes will be neuroplasticity changes in brain structural integrity plus functional and structural connectivity. Other secondary outcomes include walking endurance, self-care, mobility, performance of and satisfaction with individualized goals, and quality of life immediately post intervention and retention at 26 weeks after the intervention.

**Primary Outcomes** immediately post intervention at 3 weeks and retention at 26 weeks**:**

I Manual ability

II Gross motor function

**Secondary Outcomes** at 3 and 26 weeks**:**

III Brain structural integrity and connectivity

IV Walking endurance

V Bimanual hand performance

VI Self-Care and Mobility

VII Performance and satisfaction with individualized occupational performance goals

VIII Quality of life

### Primary Objectives

**PRIMARY HYPOTHESIS**

For children with bilateral CP, HABIT-ILE will be more effective than a waitlist control group receiving usual care to improve:

[i] manual ability on the ABILHAND-KIDS by a difference of 1.6 logits and

[ii] gross motor function on the Gross Motor Function Measure (GMFM-66) by a difference of 5 points.

**SECONDARY HYPOTHESES**

For children with bilateral CP, HABIT-ILE will be more effective than a waitlist control group receiving usual care to increase:

[iii] Brain structural integrity measured using fMRI guided tractography13;

[iv] Walking endurance (6 Minute Walk Test: 6MWT)16;

[v] Bimanual hand performance (Both Hands Assessment: BoHA)

[vi] Self care and mobility (Pediatric Evaluation of Disability Inventory Computer Adapted Test: PEDI-CAT)17;

[vii] Performance and satisfaction scores on the Canadian Occupational Performance Measure (COPM)18.

(viii) Quality of Life (Cerebral Palsy Quality of Life Questionnaire – CPQOL, parent proxy and child report; and **The Child Health Utility Index** CHU9).

### Outcome Measures

Three measurement time points will be taken: baseline (T1); immediately post intervention ***primary endpoint*** (T2); 26 weeks post intervention ***retention*** (T3). Children allocated to the waitlist group will be offered HABIT-ILE following the 6 month retention time point.

***Hypotheses I:*** *HABIT-ILE will be more effective than a waitlist control group receiving usual care to [i] improve manual ability on the ABILHAND-KIDS and [ii] gross motor function on the Gross Motor Function Measure (GMFM-66).*

**Primary outcomes at Primary End-Point (T2) and retention (T3):**

I. **ABILHAND-Kids** is a Rasch-built parent completed questionnaire measuring manual ability of children with CP. The ABILHAND-KIDS has demonstrated content, construct and evaluative validity, high internal consistency (α=0.94), excellent test retest reliability (r=0.91)37 and is responsive in detecting change following intensive upper limb motor training interventions (SDD= 0.81-1.03 logits)38,39. The ABILHANDS has the strongest evidence of validity and reliability to measure hand function in children with bilateral CP40.

II. The **GMFM-66** is a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP41. The GMFM-66 has established construct validity, high test retest reliability (ICC 0.99)41 and is responsive to change (MCID=1.5)41-43.

***Hypotheses II****: HABIT-ILE will be more effective than a waitlist control group receiving usual care to increase brain structural integrity and connectivity*

**Secondary outcomes:**

***III* Brain Structural Integrity**

Brain MRI will be conducted using 3T scanners. The child will be familiarised with the MRI procedures before the scan. During the MRI, the child will watch an age-appropriate movie of their choice, except during the acquisition of the functional MRI. Structural brain images will be acquired using high-resolution 3D T1-weighted MPRAGE and high-resolution 3D T2-weighted FLAIR. Diffusion MRI data will be acquired using a multi-shell approach with 20 directions at b=1000s/mm2 and 60 directions at b=3000s/mm2. Functional MRI data will be acquired using a block design, with a simple hand and foot tapping task. The total scan time will be <1hour.

Structural brain images will be used for lesion scoring using the Fiori scale, a semi-quantitative scale for use in brain imaging of cerebral palsy. Structural brain images will also be used to assess alterations in cortical thickness in response to therapy. These diffusion data will allow both traditional analysis using the diffusion tensor model (fractional anisotropy and mean diffusivity), as well as state-of-the-art tractography and calculation of advanced imaging microstructural biomarkers thought to closely reflect the status of the underlying brain tissue. fMRI guided tractography will be carried out as described previously34,54.

***IV Walking Endurance***

The Six Minute Walk Test is a clinical exercise test measuring walking endurance with excellent test retest reliability (ICC 0.98) for children with CP16. The test requires participants to walk as far as possible in six minutes using a 10 meter track with cones demarcating the turning points. Participants will be given verbal and visual instructions before testing. Participants will be instructed to walk as far as possible without running in six minutes. Participants will be given verbal encouragement and every 30 seconds will be advised of the distance covered (in laps) and the time remaining. Distance will be measured to the nearest five-meter mark.

***V Bimanual Hand Performance***

The Both Hands Assessment (BoHA) measures how children who have bilateral CP use their hands together in bimanual activities. The measure was developed through adaptation of the Assisting Hand Assessment17. Rasch measurement modelling showed strong evidence of internal construct validity, with two separate item difficulty hierarchies; for children with (a) symmetric upper limb use; (b) asymmetric upper limb use17. The test uses a selection of toys to elicit bimanual hand behavior and can be administered in a structured play session or using the board game version depending on the age of the child. The BoHA takes 15 minutes to complete. The assessment is video-taped for later scoring by a rater blinded to group allocation and who has been certified in its use.

***VI* Self-Care and Mobility**

**Pediatric Evaluation of Disability Inventory Computerised Assessment Test (PEDI-CAT):** The PEDI-CAT is a standardised, norm-referenced assessment of independence in self-care. The test is valid, reliable and responsive in this population18. The PEDi-CAT is completed by parents using an ipad application. The item bank of the PEDI-CAT was developed using Rasch measurement modelling on large samples of typically developing children and those with disabilities. Two domains, Self-Care and Mobility will be completed by caregivers.

**VII Performance and satisfaction with occupational performance goals.**

**The Canadian Occupational Performance Measure (COPM)**19 will be used to measure performance of and satisfaction with individually defined self-care, leisure or productivity goals. Test retest reliability is high (ICC 0.76-0.89) and the COPM is responsive to change19. Children eight years and older can self-report, and caregivers can complete the COPM for younger children or those with cognitive difficulties which would preclude then from completing it independently. Children and their caregivers will set up to three goals. Perceived performance of an individualized goal and satisfaction with performance is rated on a 1-10 scale with higher scores reflecting higher perceived performance and satisfaction.

**VIII Quality of life**

The **CP-QOL Child** is a 52-item, condition-specific self-report measure of child quality of life (QOL) that is specifically developed for measuring QOL in children with CP. The majority of items have the stem “How do you feel about…” with a response scale of 9 points from 1=very unhappy to 9=very happy. The domains covered in the child self-report version include physical wellbeing, social wellbeing, emotional wellbeing, school, and acceptance by others. It has good concurrent validity, internal consistency (Cronbach’s alpha 0.80-0.90) and test-retest reliability for children 9 years of age and over. Significant discordance exists between child and parent proxy reports in many health-related QOL instruments and the child perspective will be sought in the present study. The CP-QOL will therefore be completed by all children, including children aged 8 and children with intellectual disabilities. An adult who is not participating in the study as the primary parent/caregiver will read the questionnaire alongside the child, and clarify the meaning of the questions and response scale if necessary.

**The Child Health Utility Index (CHU9 )** is a paediatric health related quality of life measure for use in economic evaluation. The measure consists of nine questions. Children can self-report from seven years of age and parents can proxy report for their child. In this study, the CHU9 will be completed by the child’s primary caregiver48.

**6 Study Design**

### 6.1 study Design Diagram

*Figure 3: Study Design and Study Flow*

**Eligibility Screening**

**Yes.** Meets criteria - consents

**No.** Does not meet criteria or declines

**Baseline Measures** (T1)

**HABIT-ILE** (n=63)

**Control** (n=63)

**Primary outcome-point** (T2) post

**HABIT-ILE**

**Post** **intervention** (T4)

**Retention:** 6 months (T3)

**Stratification and randomisation** (n=126)

Fig 3 CONSORT Trial Flow

###  Study Design

**Type of Study*:***

This study is a pragmatic, randomised waitlist controlled trial (RCT) in 126 children with bilateral cerebral palsy, which aims to evaluate the effects of HABIT-ILE versus usual care on manual ability and gross motor function immediately post intervention.

This multi-site randomised waitlist controlled trial has been designed according to the SPIRIT statement44, and will be reported according to the CONSORT statement45 and registered on the Australian New Zealand Clinical Trials Registry.

**Number of Participants:**

126 children with bilateral cerebral palsy, aged between six and 16 years.

**Study Sites*:***

This is a multi-centre RCT across our three collaborating centres (QLD, NSW, WA).

**Design leading to aim achievement**:

We will conduct a RCT to test the effectiveness of an integrated upper and lower limb motor training program called HABIT-ILE to improve manual ability and gross motor function in 126 children with bilateral CP. We have chosen to conduct an RCT, which is the highest quality design for answering an effectiveness of treatment research question.

**Blinding:**

All outcome assessments will be completed by physiotherapists and occupational therapists blinded to group allocation.

**Expected duration of Study*:***

Commencement once all ethics and governance approvals have been given. Study will be conducted over four years.

**Data types:**

We will collect objective data on manual ability using the ABILHAND-KIDS, gross motor function using the GMFM, brain structural integrity and connectivity using structural MRI and diffusion MRI, walking endurance using the 6MWT and bimanual hand performance using the BoHA. All measures are suitable for children with bilateral CP. One subjective measure will be collective from children and is appropriate for use with children over eight years of age and for younger children will be completed by their primary caregiver. One questionnaire-based measure of self-care performance will be collected from the child’s primary caregiver. All data are re-identifiable.

**Data collection:**

Data will be collected in one of four ways:

* Paper forms
* Online survey platform (Qualtrics) instead of/in addition to paper forms
* Devices (MRI, photo/video/audio recording devices) owned by sites/organisations (not personal devices)
* Face-to-face assessments with the child

**Data transfer:**

Data will be transferred securely in one of the following ways:

* Data collected on Qualtrics (electronic) will be downloaded and stored on the secure QCPRRC research server and uploaded to RedCap
* Data collected on paper forms will be converted into an electronic format by the site therapist, forwarded using a secure file transfer service such as CloudStor and stored on the secure QCPRRC research server or uploaded directly to RedCap. Original paper files will be sent to QCPRRC via registered post or courier after being de-identified at the conclusion of the data collection phase
* Data collected from devices will be downloaded from devices by the site therapist, forwarded using a secure file transfer service such as CloudStor and stored on the secure QCPRRC research server or uploaded directly to RedCap, then deleted.

**Data storage:**

Data (both working and archived data) recorded on paper will be stored the trial sites in locked filing cabinets during the data collection phase and within an archive box located in the locked filing cabinets of investigators at the Centre for Children’s Health Research, South Brisbane Australia (Dr Leanne Sakzewski, Professor Roslyn Boyd) at the conclusion of the data collection phase. Data will be stored on secure Australian servers using RedCap (database) and the secure QPCRRC research server. Data will not be destroyed. De-identified MRI scans will be sent securely to the Australian E-Health Research Centre, CSIRO. MRI data will be stored on a local secure server at CSIRO.

***ix. Timelines:***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Year 1****2018** | **Year 2****2019** | **Year 3****2020** | **Year 4****2021** |
| Finalise Manual of Operations |  |  |  |  |
| Appoint IDSMC  |  |  |  |  |
| Complete human ethics |  |  |  |  |
| Recruit coordination staff and therapists |  |  |  |  |
| Educate therapists to ensure HABIT-ILE fidelity |  |  |  |  |
| Recruit participants |  |  |  |  |  |
| Treat participants and collect data |  |  |  |  |  |
| Analysis, write up and publication |  |  |  |  |

**Contingencies:**

We do not anticipate problems with our plan to recruit 126 children across 3 sites. The waitlist design ensures that all participants receive the intervention, thereby enhancing recruitment. A two week intensive model of HABIT-ILE will enable children from regional centres to access HABIT-ILE. The CIs and AIs have a strong track record of successfully completing NHMRC trials, with all studies achieving recruitment targets4,6,51-53. Data from the Australian Cerebral Palsy Register indicates 1240 potentially eligible children reside in the 3 recruiting states, therefore recruitment is highly feasible.

**Students:**

This study may involve research higher degree students, who would be identified by CIs. Students would not be involved in the primary analysis of the study, but on peripheral aspects.

**Study visits:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Assessment/Procedure** | **T1 Baseline Assessment** | **T2 Follow-up Assessment 3 weeks** | **T3 Follow-up Assessment 26 weeks** | **T4 Follow-up Assessment Waitlist group only** |
| Informed Consent | **x** |  |  |  |
| Demographic Information  | **x** |  |  |  |
| **Primary Outcome** |
| GMFM | **x** | **x** | **x** | **x** |
| ABILHAND Kids | **x** | **x** | **x** | **x** |
| **Secondary Outcomes** |  |  |  |  |
| Neuroimaging | **x** | **x** | **x**  |  **x** |
| 6MWT | **x** | **x** | **x** | **x** |
| BoHA | **x** | **x** | **x** | **x** |
| PEDI-CAT (P) | **x** | **x** | **x** | **x** |
| COPM  | **x** | **x** | **x** | **x** |
|  | CPQOL (child self-report and P) | **x** | **x** | **x** | **x** |
|  | CHU9 (P) | **x** | **x** | **x** | **x** |
|  | Health Resource Usage Questionnaire | **X** | **X** | **X** | **x** |

Key: P=parent completed

###  Standard Care and Additional to Standard Care Procedures

|  |  |  |
| --- | --- | --- |
| **CONTROL Usual Care Procedures** |  | **HABIT-ILE Additional To Standard Care** |
| **Procedure** | **Time/Visit** | **Dosage/Volume** |  | **Procedure** | **Time/Visit** | **Dosage/Volume** |
| **I GMFM** | T1, T2, T3, T4  | 20mins |  |  **I PDMS-2** | T1, T2, T3 | 20mins |
| **II ABILHAND-Kids** | T1, T2, T3, T4 | 10mins |  | **II ABILHAND-Kids** | T1, T2, T3 | 10mins |
| **III MRI** | T1, T2, T3, T4 | 60mins |  | **III MRI** | T1, T2, T3 | 60mins |
| **IV 6MWT** | T1, T2, T3, T4 | 6mins |  | **IV 6MWT** | T1, T2, T3 | 6mins |
| **V BoHA** | T1, T2, T3, T4 | 15mins |  | **V BoHA** | T1, T2, T3 | 15mins |
| **VI PEDI-CAT** | T1, T2, T3, T4 | 15mins |  | **VI PEDI-CAT** | T1, T2, T3 | 15mins |
| **VII COPM** | T1, T2, T3, T4 | 20 mins |  | **VII COPM** | T1, T2, T3 | 20 mins |
| **VIII CPQOL** | T1, T2, T3, T4 | 20mins |  | **CPQOL** | T1, T2, T3 | 20mins |
| **IX CHU9** | T1, T2, T3, T4 | 10mins |  | **CHU9** | T1, T2, T3 | 10mins |
| **Therapy\*** | Variable | Variable |  | **Therapy** | Daily for 10 days | 6.5 hrs |

\* Note we cannot control whether or not standard care actually carries out therapy intervention at the recommended intensity (“dose”). This is a pragmatic trial.

### study interventions

**HABIT-ILE: Hand Arm Bimanual Intensive Training Including Lower Extremity training**

HABIT-ILE is a motor learning approach simultaneously addressing coordination of the upper and lower limbs9. Key elements of HABIT-ILE are:

***Dose:*** We will deliver a total dose of 65 hours of HABIT-ILE. The 65 hours of HABIT-ILE will be achieved through a 2 week intensive group delivered day camp for 6.5 hrs/day over 10 days conducted in the school holidays. Results for our previous research in intensive upper limb training in unilateral CP4-6 and from our systematic review of all upper limb interventions8 indicate that 60 hours is likely to be a sufficient dose to achieve significant changes in motor performance, and the two week camps are feasible for children and their families. The model of HABIT-ILE to be tested has been adapted to maximise future clinical translation to ensure acceptability and feasibility to children with bilateral CP and their families in Australia.

***Mode:*** Groups of 10-12 children delivered (1:1 or 2:1 therapist / volunteer / student to child ratio according to ability).

***Content and tailoring:* Upper extremity:** Intervention will be based on the child’s motor abilities (determined at baseline), age, interests and self-identified functional goals. Tasks/activities are made incrementally more challenging. Practice is structured, using whole task practice with high repetition and ongoing feedback about performance. Tasks that will be performed include: (i) incremented table top fine motor activities; (ii) activities of daily living when standing/walking; (iii) gross motor play and physical activities. Based on the pilot study of HABIT-ILE, we expect that 40% of the time will be spent engaged in activities requiring gross upper limb dexterity, 30% on activities of daily living, 20% manipulative games, and 10% on other card games, arts and crafts. **Lower extremity:** Based on the child’s motor abilities, postural control/sitting balance will be progressed from sitting on a stool to sitting on fitness balls to build core strength; progression of standing balance with use of balance boards. Based on the pilot study of HABIT-ILE11, we expect that sessions will be structure so that 40% of time is spent sitting on fitness balls, 20% sitting on stools, 20% standing and 20% walking/running.

***Intervention providers:*** Physiotherapists and occupational therapists delivering HABIT-ILE will complete standardised training provided by the developer of HABIT-ILE (CIC). This will coincide with the first intensive intervention camp conducted. The trained therapists will in turn train and supervise therapy students and coach parents to deliver HABIT-ILE.

***Location:*** The intervention groups will be conducted in the clinics in each of the participating sites.

**Usual Care**

Usual care over the six month wait-list period will vary for children with CP across Australia and can range from weekly clinic-based therapy sessions to school-based consultative services provided on a monthly, quarterly or yearly basis. In order to understand the variability in usual care received, all families in both groups will complete a usual care diary for the duration of study involvement. The diary (via an APP) will record the frequency and duration of physiotherapy, and occupational therapy and any other concurrent medical interventions such as intramuscular Botulinum Toxin A injections and/or serial casting. All children in the control group will be offered HABIT-ILE commencing at the subsequent school holiday following the 6 month retention time point (T3).

### Randomisation

The randomisation sequence will be computer generated centrally at the QLD site. Children will be recruited in blocks of 8-12 and stratified into 1 of 2 groups based on GMFCS (II vs. III-IV). After consent and baseline measures, children will be centrally randomised to HABIT-ILE or control intervention through a REDCAP randomisation module, determined by non-study personnel.

6.6 Health Economics evaluation

A within trial cost-utility analysis46 will be conducted to synthesize the costs and benefits of the HABIT-ILE training program compared to usual care. Resource use (staff time, equipment and facility use) associated with the program will be collected alongside the RCT. Health care utilization will be collected using a resource use questionnaire previously used in CP child studies47. Utility will be derived from the CHU-9D48, a generic child quality of life measure designed specifically for economic evaluation and which has been validated in an Australian population49. AI Dr Rowell will provide expertise in developing economic models to analyze costs and outcomes of the HABIT-ILE intervention. Incremental Cost Effectiveness Ratios (ICERs) will be estimated and where appropriate sensitivity analyses undertaken as in previous RCTs by our group50.

## **Study Population**

### Recruitment Procedure

Families with a child meeting eligibility will be invited to join the study through our three collaborating sites (QLD, NSW, WA) and associated clinical services (Lady Cilento Children’s Hospital, Cerebral Palsy Alliance, and Perth Children’s Hospital). Recruitment from three major metropolitan centres will enable the target sample size to be achieved (50 in NSW and 50 in QLD and 26 in WA). Based on numbers on the Australian Cerebral Palsy Register (1240 potentially eligible participants) and our well-established state-wide clinical networks, recruitment of 126 participants is feasible across the 3 sites.

Recruitment at each site will begin following ethical and governance approvals are obtained. Recruitment will draw upon current databases within each organization, referrals from clinical services and the Cerebral Palsy Clinical Trials Register. Contact with participants will occur via one of the following mechanisms:

1. Child name, basic characteristics, and family contact details are identified on a Clinical Trials Register, clinical and/or research database hosted by one of the partner institutions
2. Families who consent to receive information about clinical trials will be sent up to two emails and one postal package with approved trial invitation letter and flyer
	1. The Study Coordinator and/or site therapist will then follow-up with a phone call with families (at least one week later) to ascertain interest in the study
		1. Families who indicate interest will be sent the participant information and consent forms and contacted again after these have been received to discuss enrollment
		2. Families who indicate no interest will not be contacted again
3. Children and families attending a clinical service associated with the project (including the Queensland Paediatric Rehabilitation Service (QPRS at the Lady Cilento Children’s Hospital), Cerebral Palsy Alliance (CPA), and the Princess Margaret Hospital (PMH) Paediatric Rehabilitation Department) will be identified by treating clinicians and provided with a flyer
4. Electronic and standard billboards at QPRS/LCCH, CPA and PMH will display the approved flyer during the recruitment period
5. A newsletter snipped will be included in the electronic and paper newsletters distributed by QCPRRC, QPRS, CPA, and PMH
6. The flyer and trial information will be posted on the research websites for QCPRRC, CPA, and PMH
7. A facebook page will host the approved trial information and flyer and be shared and ‘liked’ organically (word of mouth referrals)

### 7.2 Inclusion Criteria

(a) diagnosed with bilateral CP (diplegia/quadriplegia), GMFCS levels II (walks with limitations) to IV (limited self-mobility but able to do a standing transfer with the assistance of 1 person);

(b) aged 6 to 16 years;

(c) ability to grasp light objects and lift more impaired arm 15cm above a table surface;

(d) able to understand instructions and complete testing.

### Exclusion Criteria

(a) uncontrolled seizures

(b) orthopaedic surgery in the six months prior to or scheduled during study period (eligible for inclusion if at least 12 months orthopedic surgery)

(c) visual impairment interfering with treatment/testing; and

(d) inability to undertake standing transfers and/or walk a few steps (with a walker).

7.4 Consent

Informed consent will be obtained from the parent of every child invited to participate. Potential participants will be provided with a copy of the participant information statement (which contains both a parent/guardian-specific version and child-specific version) after agreeing to enroll in the study via phone or email contact. Potential participants will have at least 24 hours and typically more than one week to read information about the study and decide whether or not they would like to participate. Families will be invited to ask questions and discuss any aspect of the study with the site contact, Chief Principal Investigator and/or Study Coordinator should they require more information to make a decision.

Before completing any screening or baseline questionnaires or attending the first face-face appointment, parents/guardians must return a copy of the consent form by email, mail or text message with their signature. A new copy of the consent form will be signed again at the first face-to-face meeting and countersigned by the assessing/treating therapist and a witness. This will occur after the treating/assessing therapist has explained the study again in an accessible format (verbal, written, signed AUSLAN by an interpreter) to the satisfaction of both the participating parent/guardian and child. The consent conversation including who was present and the child’s assent to participate will be recorded on the reverse of the consent form.

**Participant Safety and Withdrawal**

### Risk Management and Safety

No adverse events have been reported in previous studies of HABIT-ILE for children with unilateral or bilateral CP. This is an intensive model of therapy, so we would expect children to be fatigued by the end of each day. All staff involved in delivering the intervention in the camps will be trained and supervised by senior experienced personnel. Regular daily monitoring will occur and any discomfort reported by the child or their caregiver will be immediately responded to. MRI is a non-ionising (non-cancer causing) imaging modality. All participants will be screened for MR safety prior to MRI. Some participants may experience mild claustrophobia, as with standard clinical scans. Participants may withdraw from the imaging procedure at any time and remain in the rest of the study. In the event that imaging reveals unexpected intracranial pathology, the scan will be reviewed by Professor Alan Coulthard, Professor of Radiology at HERF. If deemed medically appropriate, the parent of the child will be notified and MRI scans shared with the child’s treating clinician (Child Neurologist/Rehabilitation specialist) to review in the public health system in the usual manner. If requested by the patient, MRIs will be made available to medical professionals associated with the case.

### Adverse Event Reporting

Any minor or major adverse event associated with HABIT-ILE will be screened on a daily basis by the treating therapist by verbal questioning and will inform the Study Coordinator and Chief Investigators (except major adverse events or those requiring medical treatment, which must be reported as soon as possible, and within 24 hours). Minor adverse events include:

* Near miss accidents (such as falling off a bike or falling heavily in a game)
* Sore muscles, bruises, other minor injuries not requiring medical treatment
* Feeling upset, guilty, or sad

Major adverse events include:

* Injuries that require medical treatment (such as moderate-severe strains or broken bones)
* Depression or anxiety

After reporting to the site Chief Investigator, local site processes will be followed as necessary. The Chief Investigators will report all AEs within 48 hours to the IDSMC. The IDSMC will review all AEs to determine appropriate actions.

The IDSMC will also review interim data in the context of similar trials at least yearly. Standard Terms of Reference will be followed.

### Handling of Withdrawals

Participants can withdraw at any time. Participants who choose to withdraw from the study will not be penalised in any way. If they wish to continue with therapy intervention for their child they will be assisted to source another local therapy option that matches their preferences. Participants are informed of their right to withdraw at any time without consequences at the time of reading participant information forms and signing of consent forms. Data will be analysed on an intention to treat basis.

Participants can enroll and receive HABIT-ILE irrespective of whether they consent to the neuroimaging aspect of the study.

### Replacements

Participants that withdraw will not be replaced, as the a priori power calculation will account for a 10% dropout rate and 10% crossover rate.

# 9 Therapist Training and Fidelity

## 9.1 Therapist Attributes

It is required that therapists possess the following attributes:

* Full registration with the Australian Health Practitioner Regulation Agency (AHPRA, Physiotherapists and Occupational Therapists) OR Full members with accreditation from Exercise & Sports Science Australia (ESSA, Exercise Physiologists)
* Current Basic First Aid and CPR certificate

It is highly desirable that therapists possess the following attributes:

* 3+ years experience working with children with cerebral palsy and their families
* Experience working within models or frameworks of motor learning

## 9.2 Therapist Training

Standardized therapist training will be provided to therapists employed to deliver the intervention. The training package will include:

* Intervention manual
* Onsite training during the first HABIT-ILE camp lead by a master trainer

Training sessions will be video recorded and accessible at any time for established or new therapists delivering the intervention

## 9.3 Fidelity

All group intervention sessions will be videotaped and a random selection viewed for fidelity adherence and competence criteria.

# Statistical Methods

### 10.1 Sample Size Estimation & Justification

A 1.6 logit change on the ABILHAND kids was achieved in the pilot study of HABIT-ILE11. A sample of 126 (63 in each arm) yields 80% power, with significance at a two-sided p value of 0.05 to show a difference of 1.6 ABILHAND Kids logits, with a standard deviation of change of 3.0 and buffering for 10% attrition. With the primary sample size of 126, we have >80% power to detect a difference of 5 points or greater on the GMFM (assuming SDD=6 and alpha=0.05, buffering for 10% attrition). Neuroimaging Outcomes: A 1% change in FA using fMRI guided tractography, and a 6% change in cortical thickness are considered realistic estimates for current therapies. Our recent work on power analysis for imaging-measures of neuroplasticity in CP suggests that, assuming an 80% success rate of MRI, 39 subjects are required to detect a 1% change in FA using fMRI guided tractography, the most sensitive available method.

10.2 Statistical Methods to be Undertaken

AI Robert Ware, Professor of Biostatistics, Griffith University, will provide expert advice for guiding and assisting with the analysis. Analyses will follow standard principles for RCTs using two-group comparisons on all participants on an intention-to-treat basis. Imputation techniques will avoid bias as a consequence of non-ignorable missing data during follow up. Primary comparison immediately post intervention (T2) based on ABILHAND-KIDS and GMFM scores will be between treatment groups using linear regression with treatment group (HABIT-ILE/waitlist control) included as the main effect and baseline ABILHAND-KIDS as the covariable. Effect estimates will be presented as mean difference and 95% confidence interval. Secondary analyses will use similar methods to compare outcomes between groups immediately post intervention (T2) for brain structural integrity and structural connectivity (dMRI and fMRI guided tractography), and at T2 and 26 weeks (T3) for clinical outcomes: walking speed, self-care and performance of and satisfaction with individualised goals. Comparisons of the extent of anatomical change in between T1 and T2 will be made between each group to quantify the relative effect of HABIT-ILE versus usual care. In cases where interval data are not able to be transformed appropriately for regression analyses, non-parametric methods (Mann-Whitney U) will be used for between-treatment comparisons. Possible differential attrition will be assessed by comparing baseline characteristics of drop-outs and continuing participants using t-tests (or Mann-Whitney U) for continuous variables and chi-squared tests for categorical variables. Sensitivity analyses of all outcomes will be conducted using multiple imputation techniques, to investigate the effect of non-ignorable missing data during follow up.

# 11. Storage of Blood and Tissue Samples

## 11.1 Details of Records

No blood and tissue samples will be taken.

# 12. Data Security & Handling

### 1 Details of where records will be kept & How long will they be stored

Progress notes taken by treating therapists will be fully identified for legal reasons but will be stored confidentially in accordance with professional code of conduct and relevant legislation.

All other information will be coded with a participant ID number. Any identification codes will be stored in a different place from the data records to which they are linked. All measurable steps will be taken to ensure that health information collected is protected at all times. Access at QCPRRC will be limited to the QCPRRC Chief Investigators and study coordinator (Dr Leanne Sakzewski, Prof Roslyn Boyd, Prof Jenny Ziviani, Ms Sarah Reedman). All consent forms and identifiable information will be stored in a separate, locked filing cabinet to the research data. Data management will comply with relevant privacy protocols, such as the Australian Standard on personal privacy protection.

### Confidentiality and Security

All information will be coded, and stored in a locked filing cabinet at Queensland Cerebral Palsy and Rehabilitation Research Centre, with the Chief Investigators and Study Coordinator the only people able to access this cabinet. All measurable steps will be taken to ensure that health information collected is protected at all times. Access at Queensland Cerebral Palsy and Rehabilitation Research Centre will be limited to the Queensland Cerebral Palsy and Rehabilitation Research Centre Chief Investigators and study coordinator (Dr Leanne Sakzewski, Prof Roslyn Boyd). Any identification codes will be stored in a different place from the data records to which they are linked.

Additionally, all consent forms and identifiable information will be stored in a separate, locked filing cabinet to the research data. Data management will comply with relevant privacy protocols, such as the Australian Standard on personal privacy protection.

Data stored in electronic form will also be stored on the Queensland Cerebral Palsy and Rehabilitation Research Centre, The University of Queensland secure server with access limited to Chief Investigators and study coordinator at the Queensland Cerebral Palsy and Rehabilitation Research Centre. De-identified MRI data will be stored on a secure local server at the Australian E-Health Research Centre, CSIRO with access limited to Chief Investigators and named investigators on ethics.

## 12.3 Data Sharing

In accordance with the NHMRC Statement on Data Sharing,

*"NHMRC encourages data sharing and providing access to data and other research outputs (metadata, analysis code, study protocols, study materials and other collected data) arising from NHMRC supported research"*

data will be made available to other researchers or funding bodies including the NHMRC as necessary for the purposes of meta-analysis/systematic review and/or confirmation of statistical results. This data will be made available at group-level. If individual level data are required, a limited, codified dataset will be made available to reduce or eliminate the possibility of re-identification of the data.

A description of the dataset (metadata) will be published so that it can be discovered and/or cited. Data will be shared directly with individuals or institutions that approach the custodians. Future use and sharing of data is addressed on the Parent Information Sheet. Identifiable data will not be available for future use unless by separate ethics application.

1. **Ethics and Dissemination**

13.1 Ethics

This project has received ethical approval from the following committees:

This project has received ethical approval from the following committees:

|  |  |
| --- | --- |
| Ethics Committee | Approval Number |
| CHQ HHS HREC |  |
| UQ MREC |  |

## 13.2 Dissemination

Results of the study will be published in:

* Conference abstracts and presentations
* Peer-reviewed articles in scientific journals
* Participant, organisation, and institution newsletters and media releases

At the conclusion of the study after the primary analyses, a summary flyer of the main outcomes of the study will be emailed and/or mailed to participants.

# Appendix

**List of Attachments included:**

|  |  |  |
| --- | --- | --- |
| **Document Name** | **Version Number** | **Date (e.g., 18 January 2012)** |
| **CHILD OUTCOME STANDARDISED ASSESSMENTS** |
| **A. ABILHAND-KIDS** | 1.0 |  November 2017 |
| **B. GMFM** | 1.0 | November 2017 |
| **C. BoHA** | 1.0 | November 2017 |
| **D. COPM record sheet** | 1.0 | November 2017 |
| **E. CPQOL child and parent proxy report** |  |  |
| **SCREENING** |
| **Demographic Questionnaire** | 1.0 | November 2017 |
| **COVARIATES** |
| **E. CHU9** | 1.0 | November 2017 |
| **Health Resource Use Questionnaire** | 1.0 | November 2017 |
| **ADVERTISEMENT** |
| **F. Study Advertisement** | 1.0 | November 2017 |
| **G. Telephone Script** | 1.0 | November 2017 |

# References

1. Access Economics. The Econonic Impact of CP in Australia in 2007. Access Economics; 2008.

2. **ACPR Group**. Australian Cerebral Palsy Register Report 2016, Birth years 1993-2009. Sydney: Cerebral Palsy Alliance, 2016.

3. **Novak I**  et al. Clinical prognostic messages from a systematic review on cerebral palsy*.* *Pediatrics* 2012;130:e1285-312.

4. **Sakzewski L** et al. RCT of density and context of upper limb intensive group versus individualized occupational therapy for children with unilateral CP*.* *DMCN* 2015;57:539-47.

5. **Sakzewski L** et al. Comparison of dosage of intensive upper limb therapy for children with unilateral cerebral palsy: how big should the therapy pill be? *Res Dev Disabil* 2015;37:9-16.

6. **Sakzewski L** et al. RCT of constraint-induced movement therapy and bimanual training on activity outcomes for children with congenital hemiplegia. *DMCN* 2011; 53:313-20.

7. **James S** et al. RCT of web-based multimodal therapy for unilateral cerebral palsy to improve occupational performance*.* *DMCN*  2015;57:530-8.

8. **Sakzewski L, Boyn RN.** et al. Efficacy of upper limb therapies for unilateral cerebral palsy: A meta-analysis*.* *Pediatrics* 2014;133:e175-204.

9. **Bleyenheuft Y** et al. Hand and Arm Bimanual Intensive Therapy Including Lower Extremity in Children With Unilateral Spastic CP: A RCT*.* *Neurorehabil Neural Repair* 2014;29:645-57.

10. **Bleyenheuft Y** et al. Hand-Arm Bimanual Intensive Therapy Including Lower Extremities (HABIT-ILE) for Children with Cerebral Palsy*.* *Phys Occup Ther Pediatr* 2014;34:390-403.

11. **Bleyenheuft Y** et al. Intensive upper- and lower-extremity training for children with bilateral cerebral palsy: a quasi-randomized trial*.* *DMCN* 2017; Jan 30:[epub ahead of print].

12. Fiori S, **Boyd RN.** et al. Reliability of a novel semi-quantitative scale for classification of structural brain MRI in children with cerebral palsy*.* *DMCN* 2014;56:839-45.

13.Reid LB, **Boyd RN.** et al. Interpreting Intervention Induced Neuroplasticity with fMRI: The Case for Multimodal Imaging Strategies*.* *Neural Plast* 2016;2016:2643491.

14. Rose S, **Boyd RN.** et al. MRI structural connectivity, disruption of primary sensorimotor pathways, and hand function in cerebral palsy*.* *Brain Connectivity* 2011;1:309-16.

15. **Pannek K** et al. Assessment of the structural brain network reveals altered connectivity in children with unilateral CP*.* *NeuroImage Clinical* 2014;5:84-92.

16. Maher CA et al. The six-minute walk test for children with CP*.* *Int J Rehabil Res* 2008;31:185-8.

17. Haley SM et al. Accuracy and precision of the Pediatric Evaluation of Disability Inventory computer-adaptive tests (PEDI-CAT)*.* *DMCN* 2011;53:1100-6.

18. Law M et al. *Canadian Occupational Performance Measure.* CAOT Publications.; 1998.

19. Wake M et al. Health status of Australian children with mild to severe cerebral palsy: cross-sectional survey using the Child Health Questionnaire*.* *DMCN* 2003;45:194-9.

20. Donkervoort M et al. Determinants of functioning of adolescents and young adults with cerebral palsy. *Disabil Rehabil* 2007;29:453-63.

21. Michelson S et al. Education and employment prospects in CP. *DMCN* 2005;47:511-7.

22. **Novak I** et al. A systematic review of interventions for children with CP: state of the evidence*.* *DMCN* 2013;55:885-910.

23. Chen YP et al. Effectiveness of CIMT on upper-extremity function in children with CP: a systematic review and meta-analysis of randomized controlled trials*.* *Clin Rehabil* 2014;28:939-53.

24. Moreau NG et al. Effectiveness of Rehabilitation Interventions to Improve Gait Speed in Children With Cerebral Palsy: Systematic Review and Meta-analysis*.* *Phys Ther* 2016;96:1938-54.

25. Krageloh-Mann I et al. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *DMCN* 2007;49:144-51.

26. Reid LB, **Boyd RN** et al. Rehabilitation and neuroplasticity in children with UCP*.* *Nature Rev Neurol* 2015;11:390-400.

27. Staudt M et al. Two types of ipsilateral reorganization in congenital hemiparesis*.* *Brain* 2002;125:2222-37.

28. Kulak W et al. Neurophysiologic and neuroimaging studies of brain plasticity in children with spastic cerebral palsy*.* *Exp Neurol* 2006;198:4-11.

29. Friel KM, **Bleyenheuft Y** et al. Skilled Bimanual Training Drives Motor Cortex Plasticity in Children With Unilateral Cerebral Palsy*.* *Neurorehabil Neural Repair* 2016;30:834-44.

30. Pagnozzi AM, **Boyd RN** et al. Alterations in regional shape on ipsilateral and contralateral cortex contrast in children with unilateral cerebral palsy and are predictive of multiple outcomes*.* *Human brain Mapping* 2016;37:3588-603.

31. Reid LB, **Boyd RN** et al. Measuring Neuroplasticity Associated with Cerebral Palsy Rehabilitation: An MRI based Power Analysis*.* *Int J Dev Neurosci* 2017;Jan 24:[epub ahead of print].

32. Pagnozzi AM, **Boyd RN** et al. Automated, quantitative measures of grey and white matter lesion burden correlates with motor and cognitive function in children with unilateral cerebral palsy*.* *Neuroimage Clin* 2016;11:751-9.

33. Pagnozzi AM, **Boyd RN** et al. Optimization of MRI-based scoring scales of brain injury severity in children with unilateral cerebral palsy*.* *Pediatr Radiol* 2016;46:270-9.

34. Reid LB, **Boyd RN** et al. Surface-Based fMRI-Driven Diffusion Tractography in the Presence of Significant Brain Pathology: A Study Linking Structure and Function in CP*.* *PLoS One* 2016;11:e0159540.

35. Chan AW et al. SPIRIT 2013 statement*.* *Ann Intern Med* 2013;158:200-7.

36. Schulz KF et al. CONSORT 2010 Statement*.* *BMJ* 2010;340

37. Arnould C et al. ABILHAND-Kids. *Neurology* 2004;63:1045-52.

38. **Bleyenheuft Y** et al. Measuring changes of manual ability with ABILHAND-Kids following intensive training for children with unilateral CP. *DMCN* 2016;Nov29:[epub ahead of print]

39. de Jong LD et al. Reliability and sources of variation of the ABILHAND-Kids questionnaire in children with cerebral palsy*.* *Disabil Rehabil* 2017:1-6.

40. Elvrum AK et al. Outcome measures evaluating hand function in children with bilateral cerebral palsy: a systematic review*.* *DMCN* 2016;58:662-71.

41. Russell DJ et al. Improved scaling of the gross motor function measure for children with cerebral palsy: evidence of reliability and validity*.* *Phys Ther* 2000;80:873-85.

42. Wang HY, Yang YH. Evaluating the responsiveness of 2 versions of the gross motor function measure for children with cerebral palsy*.* *Arch Phys Med Rehabil* 2006;87:51-6.

43. Wright FVet al. Exploring the comparative responsiveness of a core set of outcome measures in a school-based conductive education programme*.* *Child Care Health Dev* 2005;31:291-302.

44. Haley SM et al. Accuracy and precision of the Pediatric Evaluation of Disability Inventory computer-adaptive tests (PEDI-CAT)*.* *DMCN* 2011;53:1100-6.

45. **Sakzewski L** et al. Clinimetric properties of participation measures for 5- to 13-year-old children with cerebral palsy: A systematic review*.* *DMCN* 2007;49:232-40.

46. Drummond M et al. *Methods for economic evaluation of health care programs*. New York, NY: Oxford University Press; 2015.

47. **Boyd RN** et al. Australian CP Child Study: protocol of a prospective population based study of motor and brain development of preschool aged children with CP*.* *BMC Neurol* 2013;13:57.

48. Stevens K. Valuation of the Child Health Utility 9D Index*.* *Pharmacoeconomics* 2012;30:729-47.

49. Ratcliffe J et al. Developing adolescent-specific health state values for economic evaluation: an application of profile case best-worst scaling to the CHU9D*.* *Pharmacoeconomics* 2012;30:713-27.

50. Comans T, **Sakzewski L, Boyd RN.** Cost-effectiveness of a web-based multimodal therapy for unilateral CP. DMCN 2017 [epub ahead of print].

51. Mitchell LE, **Boyd RN** et al. A RCT of web-based training to increase activity in children with CP*.* *DMCN* 2016;58:767-73.

52. Thomas RE, **Sakzewski L, Boyd RN** et al. Group versus individual physio following LL intra-muscular BoNT-A injections for ambulant children with CP. *Res Dev Disabil* 2016;53–54:267-78.

53. Copeland L, **Sakzewski L, Boyd RN** et al. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial*.* *J Pediatr* 2014;165:140-6.e4.

54. Pagnozzi, A. M., Dowson, N., Doecke, J., Fiori, S., Bradley, A. P., N., & Rose, S. (2017). Identifying relevant biomarkers of brain injury from structural MRI: Validation using automated approaches in children with unilateral cerebral palsy. *PloS One*, *12*(8), e0181605. doi:10.1371/journal.pone.0181605